Division of Intramural Research

NAEHS Council Update

February 2004

DIR RECRUITMENTS

Senior Clinical Investigator
The Office of Clinical Research is recruiting a tenured, senior investigator to conduct clinical research in the general area of women's reproductive health. The person selected will be board certified or eligible in obstetrics and gynecology, and will conduct a clinical research program in some aspect of disorders of women's reproductive health at the NIH Clinical Research Center in Bethesda, MD. There is particular interest in the influence of environmental factors on malignant and non-malignant disorders of women's reproductive health; examples of possible topics for study include endometriosis, polycystic ovary syndrome, uterine fibroids, infertility of various types, premature ovarian failure, microchimerism, epigenetic disorders, cancer prevention and/or vaccines. Studies will be designed to help understand basic pathophysiology and aid in the development of new treatments for these conditions. The successful candidate will be expected to have an active clinical research program in his/her specific field of interest and to play an active role in the Gynecology Consult Service at the NIH Clinical Center in Bethesda. A search committee chaired by Dr. Darryl Zeldin, Laboratory of Pulmonary Pathology, has been formed.

Senior Molecular Toxicologist
The Environmental Toxicology Program is conducting a search for a senior tenured investigator to direct research in molecular toxicology. The candidate will be expected to develop and maintain a strong intramural research effort in toxicology, particularly as it relates to defining critical target pathways, genes and cellular/molecular mechanisms of target organ responses to environmental factors and to provide programmatic leadership and council to the initiatives of the Environmental Toxicology and the National Toxicology Program in the candidate's area of expertise. Researchers in the area of developmental toxicology are particularly sought, although qualified individuals in any area of toxicological research are encouraged to apply. The Candidate should be a senior investigator with an international reputation for cutting edge research within the broad context of toxicology, an outstanding publications record, a proven history of research leadership, and demonstration of knowledge of toxicology and human health issues. The search committee chaired by Dr. Robert Maronpot, Chief of the Laboratory of Experimental Pathology, has interviewed candidates.

Tenure-track Bioinformaticist
The Biostatistics Branch is conducting a nationwide search for a tenure-track investigator with training and experience in bioinformatics. The person selected will focus activities upon developing novel methods related to toxicogenomics, such as developing and evaluating data mining approaches for elucidating characteristic patterns in gene expression array or proteomic data in order to facilitate searches for functionally-coordinated families of genes related to disease processes or response to toxicants. Improved quantitative methods for functional genomics and data mining are needed to make full scientific use of the toxicogenomics data being produced by the NIEHS

Microarray Center and the National Center for Toxicogenomics. An offer is being made to the top candidate.

Tenure-track Immunologist
The Laboratory of Pulmonary Pathobiology is conducting a national search for a cellular/molecular immunologist. The candidate will be expected to establish a high-quality independent research program in pulmonary immunology in a laboratory with diverse research interests and backgrounds. The successful candidate will have research strengths in, but not necessarily limited to, pulmonary biology (such as mechanisms of tolerance, allergy, adaptive and/or innate immune response to respiratory infections, etc). Dr. Farhad Imani, currently an Assistant Professor of Medicine at the Johns Hopkins University School of Medicine, has accepted this position.

Tenure-track Environmental Epidemiologist
The Epidemiology Branch has conducted a national search for an environmental epidemiologist. This person will be expected to develop an outstanding research program on the effects of environmental exposures and risks of chronic disease. Dr. Honglei Chen, currently an Instructor at the Harvard School of Public Health, has accepted this position.

Tenure-track or Tenured Biostatistician
The Biostatistics Branch has conducted an international search for a tenure-track or tenured statistician to conduct independent research on methods development in statistical genetics. The successful candidate will be expected to develop statistical methods for family-based studies aimed at identifying and mapping genes that influence risk modifying quantitative traits or diseases or that interact with the environmental agents that cause human disease. An offer has been extended to a leading candidate.

Tenure-track Investigator - Embryonic Stem Cell Biology
The Laboratory of Molecular Carcinogenesis is conducting a national search for a Tenure-Track Investigator in embryonic stem cell biology with research strengths in, but not necessarily limited to, development and epigenetics. The search committee, chaired by Dr. Jean Harry, Acting Chief, Laboratory of Molecular Toxicology, is interviewing candidates.

Tenure-track Investigator - Cancer Biology
The Laboratory of Molecular Carcinogenesis is conducting a national search to recruit a Tenure-Track Investigator in cancer biologist with research strengths in, but not necessarily limited to, chromatin, transcription, and epigenetics. The search committee, chaired by Dr.Michael Resnick, Laboratory of Molecular Genetics, is interviewing candidates.

Tenure-track Investigator—Endocrinology
The Laboratory of Reproductive and Developmental Toxicology is conducting a national search for a Tenure-Track Investigator in hypothalamic–pituitary–gonadal reproductive neuroendocrinology. The individual selected for this position will have a record of accomplishments in the field of mammalian Reproductive Neuroendocrinology, with a research

emphasis on the regulation and function of the hypothalamic–pituitary–gonadal axis in reproduction. A search committee is being formed.

Deputy Director, NTP Interagency Center for the Evaluation of Alternative Toxicological Methods

The Environmental Toxicology Program is recruiting a staff scientist to serve as Deputy Director of the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods. The candidate will have responsibility for managing and overseeing external independent scientific peer review of new, revised, and alternative test methods submitted for evaluation by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). The incumbent will also work with the Director to efficiently manage and oversee all aspects of scientific and administrative activities within the Center, including validation studies and workshops; and coordinate test method reviews and other relevant activities with the ICCVAM, appropriate ICCVAM Interagency Working Groups, and other national and international regulatory and research organizations. Priority will be given to applicants with demonstrated ability to foster effective scientific review and results, and who possess a level of managerial and executive ability to create an atmosphere for maximum creativity, productivity, and cooperation. The candidate should hold a veterinary or medical degree, or a doctoral degree in toxicology or a related field, and have demonstrated credentials in scientific review, the validation of standardized toxicological test methods, and an understanding of the principles of chemical safety evaluations necessary to support public health. A search committee, chaired by Dr. Michael Shelby, National Toxicology Program has been formed.

Staff Scientist--Toxicologic Pathologist

The Laboratory of Experimental Pathology has conducted a national search for a toxicologic pathologist to provide support and peer review for the National Toxicology Program toxicity and carcinogencity studies and to provide support for NIEHS researchers. Dr. Gail Pearse, currently a Research Fellow in the Laboratory of Experimental Pathology, has accepted this position.

Staff Scientist—Pathologist/Laboratory Animal Veterinarian

The Laboratory of Experimental Pathology has conducted a national search for a laboratory animal veterinarian to provide management, oversight, production support, genetic monitoring and disease surveillance of laboratory animals for the National Toxicology Program. Dr. Angela King-Herbert , currently Attending Veterinarian and Manager of Animal Biology in the Department of Regulatory Toxicology, RJ Reynolds Company, has accepted this position.

Staff Scientist—Toxicogenomics

The National Center for Toxicogenomics (NCT) of the National Institute of Environmental Health Sciences is conducting a national search for a Staff Scientist to lead a core facility to support a research program to direct the basic research applications of gene expression technologies within the NCT. The NCT is conducting an aggressive research program to apply genomic technology to toxicology and to facilitate the identification of biomarkers of specific adverse effects of exposure to environmental

agents including drugs, chemicals, and stressors. The activities of the Center will enable other investigators to probe the complexities of the mechanisms of normal genetic and metabolic pathways and to subsequently learn how diseases occur when these pathways malfunction. The position will be filled at the level of a Staff Scientist who will work in support of existing research programs in the Institute's Division of Intramural Research. The search committee, chaired by Dr. Elizabeth Murphy, Laboratory of Signal Transduction, is interviewing candidates.

Staff Scientist--Epidemiology

The Epidemiology Branch of the NIEHS is seeking a staff scientist with interests in breast cancer, genetic susceptibility and biomarkers of exposure to be the project director for the Sisters Study, a large cohort study of genetic and environmental risk factors of breast cancer. Primary duties will include maintenance of a large specimen bank, oversight of data collection and fieldwork, data analysis and publication. The incumbent will serve as the interface among Branch, laboratory and contract support staff, will serve on the Steering Committee for the study, participate in priority setting for use of study data as well as collection of new data, and will conduct research using the cohort data. While the primary focus of the study is breast cancer, it will be possible to carry out research on other outcomes within the cohort. A search committee chaired by Dr. Barbara Davis, Acting Chief, Laboratory of Women's Health has been formed

Staff Scientist—Bioethics

The Office of Clinical Research is conducting a national search for a bioethicist to be involved with health policy research on the effectiveness of federal and Institutional Review Board regulations in addressing clinical studies and clinical genetics issues. A search committee chaired by Dr. Ronald Mason, Laboratory of Pharmacology and Chemistry, is conducting interviews.

DIR RECRUITS

Dr. Joanne Promislow, Epidemiology Branch

Dr. Joanne Promislow recently joined the Epidemiology Branch at NIEHS as a tenure-track reproductive epidemiologist. Dr. Promislow was trained in physical chemistry (Ph.D. 1997, Stanford University) before becoming interested in epidemiology. Her epidemiology training was at San Diego State University and the University of North Carolina. Her research has made major contributions to two different areas: (1) the understanding of how dietary factors affect bone mineral density in the elderly residents of Rancho Bernardo, California and (2) nutritional risk factors for spontaneous abortion and preterm birth. She has also examined factors that influence bone loss during pregnancy.

At the NIEHS, Dr. Promislow is now focusing on infant nutrition. Because breast milk is the optimal source of infant nutrition and confers significant health benefits to the infant, and possibly the mother, the American Academy of Pediatrics and the World Health Organization both endorse exclusive breastfeeding for the first 6 months of life and continued breastfeeding for at least 12 months. In the United States, breast-feeding rates fall well short of these goals. Insufficient milk is the most common reason given for weaning. Dr. Promislow is interested in the physiologic determinants of milk production, which could provide valuable insights into breast-feeding practices. Human milk is also an ideal biological fluid for estimating body burdens of environmental chemicals in women and their infants, evaluating the determinants of exposure, and assessing the effect of these contaminants on the health of women and their infants. Dr. Promislow is interested in the elimination kinetics of chemicals from the mother during breast-feeding, a better understanding of which is essential to more effectively evaluate infant exposures and potential health effects. Menstrual cycle function, as a route by which environmental factors could affect women's health, is another topic of interest for.

Selected Publications

Promislow JHE, Makarushka CM, Gorman JR, Howards PP, Savitz DA, Hartmann KE. Recruitment for a Community-Based Study of Early Pregnancy: The Right from the Start Study. (in press, Paediatr Perinat Epidemiol).

Siega-Riz AM, Promislow JHE, Savitz DA, Thorp JM, Jr., McDonald T. Vitamin C intake and the risk of preterm delivery. Am J Obstet Gynecol 2003;189:519-25.

Promislow JHE, Goodman-Gruen D, Slymen DJ, Barrett-Connor E. Retinol intake and bone mineral density in the elderly: The Rancho Bernardo Study. J Bone Miner Res 2002;17:1349-58.

Promislow JHE, Goodman-Gruen D, Slymen DJ, Barrett-Connor E. Protein consumption and bone mineral density in the elderly: The Rancho Bernardo Study. Am J Epidemiol 2002;155:636-44.

Training and Mentoring

The Fellows Award for Research Excellence

The Fellows Award for Research Excellence (FARE) was started in 1995 to recognize scientific excellence among NIH intramural trainees. Trainees submit an abstract of their research, which is peer reviewed. The awards are funded by the Scientific Directors, the Office of Research on Women's Health, and the Office of Education. In 2003, 972 applications were received and 243 were funded with $1000 travel awards to attend a meeting in the United States at which they presented their abstract, either as a poster or a seminar. FARE winners will be invited also to present their work at one of the FARE poster sessions that will follow each of the Wednesday Afternoon Lecture Seminars in Bethesda, and to serve as a judge for the FARE competition next year.

The NIEHS had 14 winners of FARE awards:

Winner	*Laboratory/Branch*	*Mentor*	*Abstract Title*
Bjoern Bauer	Laboratory of Pharmacology and Chemistry	David Miller	The nuclear xenobiotic receptor, PXR, upregulates p-glycoprotein at the blood-brain barrier
Michelle Carey	Laboratory of Pulmonary Pathobiology	Darryl Zeldin	Attenuated immune response and enhanced mortality following influenza virus infection in cyclooxygenase-2 null mice
Gloria David	Laboratory of Pulmonary Pathobiology	Stephanie London	NQO1 and GSTM1 polymorphisms and childhood asthma in a high ozone area: Mexico City
Bonnie Deroo	Laboratory of Reproductive and Developmental Toxicology	Kenneth Korach	Estrogen treatment reduces expression of thioredoxin interacting protein in the mouse uterus through an estrogen-receptor independent mechanism
Marcela Hermoso	Laboratory of Signal Transduction	John Cidlowski	Glucocorticoids and tumor necrosis factor α synergistically regulate Toll-Like Receptor 2 gene expression
Joseph Lundquist	Laboratory of Molecular Toxicology	Serena Dudek	Covalently Bound Extracellular Signal Regulated Kinase Components Revealed Through LTP-Inducing Stimuli

Jeanelle Martinez	Laboratory of Computational Biology and Risk Analysis	Christopher Portier	Up-regulation of EGR-1, a growth regulatory transcription factor by TCDD in human lung cells
Scott McCulloch	Laboratory of Molecular Genetics	Thomas Kunkel	Amino acid substitutions at conserved tyrosine 52 after fidelity and bypass efficiency of human DNA polymerase Eta \
Richard Morris	Biostatistics Branch	Norm Kaplan	Testing for association in nuclear families in the presence of genotyping errors using SNP haplotypes
Francesca Storici	Laboratory of Molecular Genetics	Michael Resnick	Chromosal site-specific double-strand breaks are efficiently targeted for repair by oligonucleotides
Paul Terry	Epidemiology Branch	Jack Taylor	Ancient African haplotypes simplify the study of genetic variation and disease
Daniel Tomso	Laboratory of Computational Biology and Risk Analysis	Doug Bell	Detection of Polymorphic p53 Binding Sites in the Human Genome
Mohamed Trebak	Laboratory of Signal Transduction	Jim Putney	Reciprocal regulation of receptor-activated TRPC3 channels by diacylglycerol and protein kinase C
Jeffrey Vargason	Laboratory of Structural Biology	Traci Hall	Crystal structure and binding specificity of an RNA silencing suppressor

DIR AWARDS AND HONORS

Dr. David Armstrong (Laboratory of Signal Transduction) was named a Guest Professor in the Department of Molecular Neurobiology at the University of Salzburg and will give a course on cell signaling in the nervous system.

Dr. Lutz Birnbaumer (Laboratory of Signal Transduction and Scientific Director) delivered the 2003 "Conferencia Orias" of the Biology Society of Cordoba in Cordoba, Argentina.

Dr. Gary Boorman (Laboratory of Experimental Pathology) will chair a scientific session on "Understanding and Diagnosing Disease Using Large-Scale Differential Gene Expression Technology" at the annual meeting of the Society of Toxicologic Pathology in Salt Lake City in June 2004.

Dr. Jan Drake (Chief, Laboratory of Molecular Genetics) was elected President of the International Genetics Federation for 2003-2008.

Dr. David Dunson (Biostatistics Branch) won the "Best Paper Award" from the American Academy of Fertility Care Professionals.

Dr. E. Mitch Eddy (Laboratory of Reproductive and Developmental Toxicology) was elected to the Board of Directors, American Society for the Study of Reproduction (2002-2005) and the Executive Council, American Society of Andrology (2003-2006); appointed Associate Editor of Biology of Reproduction; and invited to be an Australian Research Centre Scholar, Australian Centre of Excellence in Biotechnology and Development, Monash Institute of Reproduction and Development, Monash University in 2004.

Dr. Ken Korach (Chief, Laboratory of Reproductive and Developmental Toxicology) was elected to the Editorial Board of the Journal of Molecular Endocrinology by the British Society of Endocrinology, presented the 2003 University Lecture for University of Texas Southwest Medical Center, and was selected as the 30th University of Maryland-Johns Hopkins Lecturer in Reproductive Biology.

Dr. Ronald Mason (Laboratory of Pharmacology and Chemistry) gave the Lawrence H. Piette Memorial Lecture, at the 44th Rocky Mountain Conference on Analytical Chemistry - Denver, CO entitled "In Vivo Lipid-derived Free Radical Formation by NADPH Oxidase in Acute Lung Injury Induced by Lipopolysaccharide - a Model for ARDS."

Dr. Bob Maronpot (Laboratory of Experimental Pathology) has been invited to present the 22nd annual Kuna Lecture at Rutgers University/University of Medicine and Dentistry of New Jersey in April 2004 and as the keynote speaker at the Dutch Society of Toxicology annual meeting in June 2004. He has also been invited to present a talk at the British Society of Toxicology annual meeting in Edinburgh, Scotland, in April 2004 and will chair a scientific session on "Hepatic Morphology and Pathophysiology" at the annual meeting of the Society of Toxicologic Pathology in Salt Lake City in June 2004.

Dr. Ron Melnick (National Toxicology Program) has been named to Who's Who in America.

Dr. Fred Miller gave the Kovacs Lecture at the Royal Society of Medicine, London, UK in March 2003 entitled "New Developments in Pathogenesis and Therapy of the Idiopathic Inflammatory Myopathies".

Dr. Christopher Portier (Chief, Laboratory of Computational Biology and Risk Analysis) was selected to give the Keynote Lecture, Conference on Mechanistic Modeling of Carcinogenesis, Japanese Biometrics Society and Radiation Effects Research Foundation, Kyoto, Japan, March 2003.

Dr. Lisa Rider (Office of Clinical Research) gave the Schlager Family Visiting Professor Lectureship in Juvenile Dermatomyositis at Children's Hospital, Boston, MA in April, 2003 entitled "Juvenile Idiopathic Inflammatory Myopathies: Lessons from the Children."

Dr. Dale Sandler (Epidemiology Branch) received the 2003 Leadership and Distinguished Service Award form the American College of Epidemiology

Dr. Steven Shears (Laboratory of Signal Transduction) was named keynote speaker at the second Japan/Korea conference on cellular signaling, held at Kyushu University, Fukuoka, Japan in June 2003 and appointed to the editorial board of the reviews journal *Essays in Biochemistry*.

Dr. Raymond Tennant (Director, National Center for Toxicogenomics) served as the Co-Chair of the Inaugural Gordon Conference on Toxicogenomics held at Bates College, Lewiston, Maine in June 2003 and was the Keynote Speaker at the NordTox Meeting in Bornholm, Denmark in June 2003.

Dr. Samuel Wilson (Deputy Director and Laboratory of Structural Biology) was the Keynote Speaker at the American Chemistry Council-LRI First Annual Science Meeting and at the Gordon Research Conference on Toxicogenomics; served as a member of the Editorial Board for the Annual Reviews of Medicine and as an Associate Editor for DNA Repair; and served on the Program Committee for the 9th International Conference on Environmental Mutagens, San Francisco, CA; as the Co-Chair of the Biannual US-EU DNA Repair Meeting; as Director of the Radiation Effects Research Foundation (A Cooperative Japan-United States Research Organization managed in the US by the NAS); and as Co-chair of "Advances in Toxicogenomics: NIEHS National Center for Toxicogenomics," a Symposium at the Society of Toxicology Annual Meeting in March 2003.

Dr. Jerrel Yakel (Laboratory of Signal Transduction) has been named to the Editorial Board of the Journal of Molecular Neuroscience.

Dr. Darryl Zeldin (Laboratory of Pulmonary Pathobiology) was named to the Editorial Board of the journal Prostaglandins and Other Lipid Mediators

National Toxicology Program
Update February 2004

Toxicology in the 21st Century: The Role of the National Toxicology Program

The last decade of the 20th century and the turn of the 21st century have produced dramatic technological advances in molecular biology and computer science. In an effort to determine how best to incorporate these new scientific technologies into its research and testing strategies and to broaden scientific knowledge linking mechanism and disease, the National Toxicology Program (NTP) has developed a vision (see attached write-up).

> *The NTP Vision for the 21st Century is to move toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations.*

The NTP will develop a roadmap or framework to guide the program in implementing its vision. The goal of the roadmap is to position the NTP strategically at the forefront of toxicology in providing scientific data and its interpretation for public health decision-making. In developing the roadmap and milestones toward achieving the vision, the NTP seeks input from all interested stakeholders on issues raised by the following questions:

- *What scientific information should the NTP be producing and what technical capabilities should the NTP have by 2008? By 2013?*
- *How do you envision that the refinement/replacement of classical toxicological studies with mechanism-based assays will impact on the evaluation of public health hazards?*
- *How can we best structure the NTP to provide this information and to ensure its optimal utilization in the protection of public health?*
- *What resources will be needed to realize this vision and how long will it take?*

Vision Activities

On Thursday, January 29, 2004, the NTP held a public meeting to receive comment on the vision and input for a roadmap. This meeting was held at the Lister Hill Center Auditorium (Building 38A), National Library of Medicine, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD, 20892. The meeting was chaired by Dr. Hillary Carpenter, Minnesota Department of Health and member of the NTP Board of Scientific Counselors, and began with an introductory presentation on the NTP vision and roadmap activities by Dr. Christopher Portier, Associate Director of the NTP. These activities include, receiving reports from three groups: an internal NIEHS Working Group, the NTP Executive Committee Working Group, and the NTP Board of Scientific Counselors Working Group, that are independently developing input on the roadmap, holding a retreat this summer, and providing opportunities for additional input by the public and NTP advisory groups. The NTP plans to hold a retreat this summer and rollout the roadmap for the vision in the fall.

A panel composed of the NTP Board of Scientific Counselors Working Group and the chairs of the NIEHS and NTP Executive Committee Working Groups received the public comments. Eight speakers presented oral public comments. Information about this meeting, including copies of any comments received, is posted on the NTP web site at http://ntp-server.nih.gov.

Report on Carcinogens Public Meeting

The NTP held a public meeting on January 27-28, 2004, to receive public comment on the current process for reviewing nominations for listing in or delisting from the Report on Carcinogens (RoC) and on the current listing criteria used for evaluating the nominations. The purpose of this meeting was to obtain input and provide all interested parties the opportunity to express their views and/or to comment on the views expressed by others. All interested parties were invited to participate. A panel that included NTP staff, representatives of the NTP Board of Scientific Counselors and the NTP Executive Committee received the public comments and participate in the discussion.

The meeting was held at the Lister Hill Center Auditorium (Bldg. 38A), National Library of Medicine, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland, 20892. Six speakers presented oral comments. Information about this meeting, including copies of public comments received, is posted on the NTP web site at http://ntp-server.niehs.nih.gov.

NTP Board of Scientific Counselors Technical Reports Review Subcommittee

The NTP Board of Scientific Counselors Technical Reports Review Subcommittee will meet February 17-18, 2004, in the Rodbell Auditorium, Rall Building at the National Institute of Environmental Health Sciences, 111 T. W. Alexander Drive, Research Triangle Park, NC. The meeting will begin at 8:30 a.m. and is open to the public. The primary agenda topic is the peer review of seven draft NTP Technical Reports, as listed below.

TR#	Chemical
494	Anthraquinone*
520	3,3',4,4',5-Polychlorinated biphenyl 26 (PCB 126)
521	2,3,7,8, Tetrachloro-*p*-dibenzene dioxin (TCDD)
525	2,3,4,7,8-Pentachlorodibenzofuran (PeCDF)
526	Dioxin mixture: (PCB 126, TCDD and PeCDF)
527	Malachite Green & Leucomalachite Green
528	1,2,3-Trichloropropane, 2,2-Bis(bromomethyl)-*p*-1,3-propanediol and Nitromethane**

* The Subcommittee reviewed the draft NTP Technical Report on Anthraquinone in May 1999. Subsequent to that peer review, the tested anthraquinone was found to contain a 0.1% contaminant. As a result, additional mutagenicity and metabolism studies were conducted and the findings from those studies are included in the revised draft report. The Subcommittee will evaluate the results from the follow-up studies, use that information to re-examine the carcinogenicity findings from the 2-year studies and make a recommendation on the carcinogenicity of anthraquinone.

**Studies of these compounds are being done in two species of fish (Medaka and Guppy).

The draft NTP Technical Reports will be available for public review, free of charge, through ehpOnline (http://ehp.niehs.nih.gov/).

The public is invited to submit written comments on any report and/or to attend the meeting and give oral comments. Additional details about the meeting, as available, are posted on the NTP web site (http://ntp-server.niehs.nih.gov *see* What's New?).

Scientific Advisory Committee on Alternative Toxicological Methods

The next meeting of the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) will be held on March 10-11, 2004, at the Hyatt Regency Hotel, One Bethesda Metro Center, Bethesda, Maryland 20814. The meeting begins each day at 8:30 a.m. until adjournment and is open to the public.

Topics included on the preliminary agenda include updates on activities of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the Interagency Coordinating Committee on Alternative Methods (ICCVAM), nominations of alternative toxicological methods, a workshop on toxicogenomics, validation of genetically modified mouse models, and performance standards for *in vitro* corrosivity test methods. The agenda and other details of the meeting, as available, will be announced in the Federal Register and posted on the NTP web site (http//:ntp-server@niehs.nih.gov *select* What's New).

The SACATM is a federally chartered advisory committee that provides input to the NIEHS Director, NICEATM and ICCVAM on the statutorily mandated duties of ICCVAM and NICEATM activities. The committee is comprised of 15 members and was established in January 2002.

NTP Interagency Center for the Evaluation of Alternative Toxicological Methods

Updated ICCVAM Submission Guidelines

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) announces the availability of the publication, "ICCVAM Guidelines for Nomination and Submission of New, Revised, and Alternative Test Methods," September 2003, NIH Publication No. 03-4508. The guidelines are an updated version of guidelines published by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) in 1999. The ICCVAM guidelines provide information to sponsors and nominators of new test methods on the framework for organizing the information and the mechanism by which ICCVAM evaluates the validation status of new, revised and/or alternative test methods proposed for regulatory testing use. This framework can also be used to organize information in support of test methods nominated for further evaluation, including proposals for validation studies. The updated ICCVAM guidelines are available electronically (PDF and HTML) on the NICEATM/ICCVAM web site at http:// iccvam.niehs.nih.gov/methods/udp.htm and a limited number of printed guidelines are available from the NICEATM (see contact information).

The ICCVAM established in 1997 coordinates the interagency technical review of new, revised, and alternative test methods of interagency interest, and coordinates cross-agency issues relating to the validation, acceptance, and national/international harmonization of toxicological testing methods. ICCVAM is as a permanent interagency committee of the NIEHS under the NICEATM (ICCVAM Authorization Act of 2000, Public Law 106-545). The Committee is composed of representatives from fifteen federal regulatory and research agencies that use or generate toxicological information. ICCVAM promotes the scientific validation and regulatory acceptance of toxicological test methods that will improve agencies' ability to accurately assess the safety or hazards of chemicals and various types of products, while refining (less pain and distress), reducing, and replacing animal use wherever possible.

NICEATM administers the ICCVAM and provides scientific and operational support for ICCVAM and ICCVAM-related activities. NICEATM and ICCVAM work collaboratively to evaluate new and improved test methods applicable to the needs of Federal agencies. Additional information about ICCVAM and NICEATM can be found at the following web site: http://iccvam.niehs.nih.gov

Responses from Federal Agencies to ICCVAM Test Recommendations

The ICCVAM Authorization Act of 2000 requires appropriate federal agencies to review test recommendations from ICCVAM and notify the ICCVAM in writing of their findings, including the identification of relevant test methods for which the ICCVAM test recommendations may be added or substituted. The agencies were sent ICCVAM test recommendations for l) *in vitro* methods for assessing acute systemic toxicity and 2) the revised Up-and-Down Procedure (UDP) for determining acute toxicity. Their responses and other current information relevant to these test recommendations are available electronically (PDF and HTML) on the NICEATM/ICCVAM web site (http://iccvam.niehs.nih.gov).

NTP Satellite Symposium on Hepatic Pathology

The NTP will sponsor a satellite symposium on Saturday, June 12, 2004, before the start of the Society of Toxicologic Pathology Annual Meeting. The annual meeting is scheduled for June 13-17, 2004. The format for the satellite symposium will the same as the one held in Savannah in 2003.

Cases will be available on a web site prior to the meeting and audience response units (for audience voting and instant display of the results) will be provided during the satellite symposium. The emphasis for the cases will be hepatic lesions although non-hepatic lesions will also be included.

Persons interested in attending can obtain information on-line at www.toxpath.org or send a message to stp@toxpath.org

NATIONAL TOXICOLOGY PROGRAM

VISION

Headquartered at the National Institute of Environmental Health Sciences • NIH • DHHS

Toxicology in the 21st Century: The Role of the National Toxicology Program

The National Toxicology Program (NTP) was established in 1978 to coordinate toxicological testing programs within the Department of Health and Human Services, develop and validate improved testing methods, develop approaches and generate data to strengthen scientific knowledge about potentially hazardous substances and communicate with stakeholders. In its 25 years of existence, NTP has become a world leader in providing scientific information that improves our nation's ability to evaluate potential human health effects from chemical and physical exposures. The NTP has maintained a number of complex, interrelated research and testing programs that provide unique and critical information needed by health regulatory and research agencies to protect public health.

The last decade of the 20th century and the turn of the 21st century have produced dramatic technological advances in molecular biology and computer science. The NTP is again ready to evaluate its key activities and in a focused and concerted effort determine how best to incorporate these new scientific technologies into its research and testing strategies and broaden scientific knowledge on the linkage between mechanism and disease. The NTP Vision for the 21st Century is to move toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations. The stimulus for the NTP Vision is to develop a framework that will promote the further development/advancement of toxicology and refine its traditional role as a predominantly observational science. Over the next year, the NTP intends to develop a roadmap for implementation of its vision that will strategically position the program at the forefront for providing scientific data and the interpretation of those data for public health decision-making.

The NTP invites all interested stakeholders to read and comment on its vision and to provide input to a roadmap for its implementation. In developing its roadmap and milestones for tasks and changes to achieve the vision, the NTP seeks input on the issues raised by the following questions:

1. What scientific information should the NTP be producing and what technical capabilities should the NTP have by 2008? By 2013?
2. How do you envision that the refinement/replacement of classical toxicological studies with mechanism-based assays will impact on the evaluation of public health hazards?
3. How can we best structure the NTP to provide this information and to ensure its optimal utilization in the protection of public health?
4. What resources will be needed to realize this vision and how long will it take?

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NTP LIAISON & SCIENTIFIC REVIEW OFFICE 919-541-0530 **E-MAIL** liaison@starbase.niehs.nih.gov

January 12, 2004

The NTP Vision for the 21st Century:

To move toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations

Since its inception in 1978, the NTP has been a leader in toxicological testing and research within the United States and contributed significantly to the scientific knowledge upon which public health decision are based. In 1995, the National Toxicology Program (NTP) initiated a program to use mechanism-based toxicology to develop, evaluate and validate better toxicological test methods. This effort has led to major changes in toxicology at the national and international level. In recent years, mechanism-based toxicology has led to some changes in the scientific basis for public-health decisions; however, it has not dramatically reduced the need for the classical tests developed in the 1970s and 80s that were the basis for many decisions related to product safety, evaluation of environmental and occupational hazards and prioritization of chemicals for further testing. It is now time to focus on changing the scientific basis for decision-making and work toward improving or replacing older classical tests with faster, mechanism-based assays.

Two activities must occur simultaneously if this change is to occur. One, we need to aggressively incorporate new laboratory methods into the NTP testing program and insure that the data produced meet the high quality standards of the NTP. Two, we need to develop strategies for the integration of new types of scientific data into the decision-making process. As a leader in toxicology, the NTP is ready to seize this challenge for improving the scientific basis for public health decision-making.

A core element of the NTP is the design, conduct, evaluation and communication of toxicological tests in a broad number of areas of concern ranging from neurotoxicity to carcinogenesis. Through the testing program, the NTP has been a leader in developing and implementing experimental designs that not only address data gaps for the agent being tested, but contribute to our fundamental understanding of toxicity in the broader context. This strength of the testing program needs to be further developed to insure that every evaluation done contributes to knowledge-based safety evaluations that use the broadest possible range of scientific evidence in reaching a decision. As new methods are developed and gain greater acceptance in developing public health decisions, our dependence on the classical testing paradigms should diminish. During this time of transition, scientific quality and clarity must be preserved to insure that decisions based solely upon new methods do not endanger the health of the public or introduce greater scientific uncertainty than the approaches used in the last century.

Only through a concerted effort focused on the linkage between mechanism and disease will toxicology achieve sufficient predictability to refine or replace disease-specific testing models with mechanism-based assays that are more informative, faster and closely linked to disease incidence and progression. This vision should enable the program to continue its leadership in toxicology and provide the scientific data and knowledge necessary for making appropriate decisions that protect (and improve) public health and the environment.

NTP Roadmap

Over the next year, the NTP intends to develop a roadmap for implementing this vision. The NTP will seek input to this roadmap from numerous groups, including its federal partners, its advisory committees and the public. In developing the framework for implementing the NTP Vision for the 21st Century, the NTP will examine its current activities, examine opportunities for modifying those activities to include recent scientific advances, identify specific activities that need to be accomplished to implement the vision and develop a framework targeted towards achieving the intent of this vision and including the necessary components for implementation, management and communication of changes in NTP activities. In developing this framework, the NTP will 1) identify the tools and technical capabilities needed to utilize new methods, models and approaches within the program; 2) develop strategies for the generation, evaluation and integration of new types of scientific data into the decision-making process; and 3) identify the resources needed to achieve both the short-term and long-term goals for the vision. The NTP will examine each mechanism through which it currently operates and evaluate its functionality toward addressing the vision. Some of the changes and directions in the roadmap will be specific to the NTP, its operations and its personnel, while others will apply to the broader field of toxicology as it is currently practiced. It is envisioned that the acceptance and implementation of this vision in addressing public health priorities will result in better science and ultimately better decisions.

NTP Mission and Goals

The mission of the NTP is to evaluate agents of public health concern by developing and applying tools of modern toxicology and molecular biology. The elements of this mission are to provide toxicological evaluations on substances of public health concern, develop and validate improved (sensitive, specific, rapid) testing methods, develop approaches and generate data to strengthen the science base for risk assessment and to communicate with stakeholders (government, public, industry, academia, environmental community) involved in the application and use of scientific data in making decisions about the safety of agents routinely encountered by humans. The overall goal of the NTP, encompassed by these mission elements, is to provide the best science possible for preventing disease due to human exposures. Unfortunately, the changing nature of biological science is such that this goal can never really be attained; however, it is a goal that requires constant diligence to insure that the tools of modern biological science are used appropriately and efficiently.

In its current manifestation, the NTP accomplishes its mission for toxicological testing through several mechanisms:

- Contract laboratories that conduct studies designed by NTP staff and contracts administered by the National Institute of Environmental Health Sciences (NIEHS)
- Collaboration and cooperation with multiple federal agencies, including toxicological research and testing at the National Center for Toxicological Research (NCTR) of the Food and Drug Administration
- Human exposure and toxicity research at the National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention
- Biological, toxicological, clinical and epidemiological research in the intramural laboratories of the Division of Intramural Research (DIR) at the NIEHS

- Research grants, contracts and interagency agreements supported through the NIEHS Division of Extramural Research and Training (DERT)
- NTP Centers, including the Report on Carcinogens, the Interagency Center for the Evaluation of Alternative Toxicological Methods, the Center for the Evaluation of Risks to Human Reproduction, and the Phototoxicology Center at the NCTR, and the NIEHS National Center for Toxicogenomics
- Collaboration and support of research with other national and international toxicology and public health agencies
- Review and evaluation of data gaps in our understanding of environmentally induced diseases through the NTP Office of Nominations
- Focused conferences and symposia, and communications to a broad spectrum of stakeholders through public meetings, electronic media and print media managed by the NTP Liaison and Scientific Review Office